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Factors Influencing Risk-based Care of the Childhood Cancer Survivor in the 21st Century

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Abstract

The population of adult survivors of childhood cancer continues to grow as survival rates improve. While it is well-established that these survivors experience a variety of complications and comorbidities related to their malignancy and treatment, this risk is modified by many factors that are not directly linked to their cancer history. Research evaluating the influence of patient-specific demographic and genetic factors, premorbid and comorbid conditions, health behaviors and aging has identified additional risk factors influencing cancer treatment-related toxicity and possible targets for intervention in this population. Furthermore, although current long-term

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follow-up guidelines comprehensively address specific therapy-related risks and provide screening recommendations, the risk profile of the population continues to evolve with ongoing modification of treatment strategies and emergence of novel therapeutics. To address the multifactorial modifiers of cancer treatment-related health risk and evolving treatment approaches, a patient-centered and risk-adapted approach to care that often requires a multidisciplinary team approach including medical and behavioral providers is necessary for this population.

Keywords

Adolescent; Antineoplastic Agents; Cancer; Child; Delivery of Health Care; Neoplasms; Risk; Survivors; Treatment Outcome

Introduction

With therapeutic advances over the past decades, 5- and 10-year survival rates for childhood cancer now exceed 80%.[1,2] This progress permits increased focus on the importance of reducing morbidity and mortality related to the prior childhood cancer experience while continuing research aimed at further increasing survival rates. In 2010 there were an estimated 379,100 survivors of childhood cancer in the United States, an increase of over 50,000 from estimates five years prior, with numbers anticipated to reach 500,000 by 2020 based on current incidence and long-term survival rates.[3] Childhood cancer survivors experience a substantial burden of chronic disease that increases in prevalence with advancing time from completion of therapy. Given the unique health risks associated with childhood cancer and its therapy, a risk-based and patient-centered care approach for individual survivors focusing on both therapeutic exposure related risks and patient-specific factors outside of treatment is recommended to anticipate and comprehensively address the complications and comorbidities affecting this growing population.[4,5]

Pediatric oncologists have pioneered risk-adapted therapy based on cancer and host characteristics in an effort to optimize disease outcomes and reduce late effects. Emerging research into primary and secondary prevention strategies is further informing risk-based care of this population. Despite this, we are only beginning to understand the complex interplay of the multiple factors contributing to morbidity in a given childhood cancer survivor. Similar to the heterogeneity of chronic and comorbid conditions in the general population, factors such as genetics, health behaviors, aging and health care access and utilization modify outcomes within the survivor population. Understanding these modifiers and how we may influence the impact of late effects through tailored primary cancer therapies and early diagnosis and intervention for late effects are key to improving the care of childhood cancer survivors into adulthood.

In this review, we will briefly discuss prior research regarding disease- and therapy-related toxicities and then explore emerging areas of survivor research that consider the complex nature of late effects and possible targets for mitigation. We will specifically address not only cancer- and therapy-related risk factors, but also genetic and patient-specific factors as they relate to risk for toxicity. Additionally, we will explore how comorbid conditions, aging, health-related behaviors, as well as health care access and utilization, influence

outcomes and should be considered in a risk-based approach to care of the childhood cancer survivor (Figure 1).

Disease and Therapy Related Toxicities

Childhood cancer encompasses a heterogeneous group of malignant conditions, arising from histologically distinct tissues. Overall, the most common types of childhood cancer include leukemia, specifically acute lymphoblastic leukemia (ALL), central nervous system (CNS) tumors and lymphomas.[1] A number of disease-specific factors impact the type and intensity of cancer therapy received, and thus risk of treatment-related toxicities. Treatment, including chemotherapeutic agents and doses, varies widely and typically involves multi-modal therapy in children with biologically aggressive or advanced malignancies. Previous research has investigated treatment-related toxicities by diagnosis and individual chemotherapeutic agent (Table 1). For example, among survivors of ALL and CNS tumors, patterns of executive functioning differ despite sharing common exposures, such as CNS-directed chemotherapy and cranial irradiation.[6] Additionally, cancer histology differs within diagnostic groups, which has implications for risk stratification and outcome. For instance, in rhabdomyosarcoma, prior studies have established that the alveolar subtype confers poor prognosis for survival, which has led to the use of more intensive treatment approaches for children with this histology compared to those with the more favorable embryonal subtype.[7]

Anticipated late effects of therapy are frequently related to age at exposure. Thus, it is relevant to note that incidence rates for diagnostic groups vary with age; Hodgkin lymphoma and bone tumors become more common as age increases, while renal and eye/orbital tumors follow the inverse pattern.[1] Genetic factors may also impact risk for late effects. Some malignancies, such as Wilms tumor, hepatoblastoma and neuroblastoma, may be associated with genetic or developmental anomalies. As a specific example, Wilms tumor and hepatoblastoma occur at increased rates in the first decade of life in children with Beckwith-Wiedemann Syndrome.[8] Other genetic anomalies or associated cancer predisposition syndromes (e.g. Li-Fraumeni Syndrome) may confer an increased lifetime cancer risk and require additional considerations during treatment planning to avoid certain exposures, such as radiation therapy.[9] Genetic and genomic testing can help assess the personal risk of cancer development based on a germline mutation, and also can be informative in predicting tumor behavior. The current molecular classification of medulloblastoma, a CNS tumor, has four distinct subgroups, WNT, SHH, group 3 and group 4, which characteristically associate with mean age of diagnosis, tumor behavior, and treatment outcomes.[10] This has motivated the development of recent clinical trials evaluating therapy reductions in the favorable risk WNT sub-group, including significantly decreased craniospinal irradiation (CSI) doses.[11]

The extent of disease and response to therapy are additional factors that affect outcomes. Greater tumor burden at diagnosis may correlate to higher stage or higher risk disease requiring more intensified therapy as compared to the patient with minimal disease. In ALL, recent studies have focused on stratification of CNS-directed therapy based on historical associations between CNS status at diagnosis with CNS relapse risk and overall survival. The Children’s Oncology Group (COG) and other groups have focused

on restricting the use of CNS irradiation to the highest risk patients and at minimal doses.[12] Others have demonstrated comparable event-free survival with elimination of cranial irradiation in first-line therapy by intensifying CNS-directed systemic and intrathecal chemotherapy.[13] Likewise, the significance of minimal residual disease (MRD) in ALL as an important prognostic indicator during induction therapy has been elucidated. The use of this technology has refined risk-directed therapy by placing increased numbers of patients in provisional low risk groups and reserving therapy intensification for poor responders.[14–16] With response-guided therapeutic modifications, we expect decreased neurocognitive deficits, as well as increased numbers of patients treated for high-risk ALL in the next generations of ALL survivors.

Late effects research has provided strong evidence for associations between therapeutic exposures and risk of specific outcomes, and in doing so has guided risk-adapted treatment, to limit exposures for those with favorable presentations, as well as surveillance strategies (Table 1). Specific toxicities for many chemotherapeutic agents are well known, such as the risk of infertility with the use of alkylating agents, cardiomyopathy associated with anthracycline use and ototoxicity related to platinum-based therapy.[17] Research has established dose-response relationships for the adverse effects from many of these agents, helping to guide therapeutic decisions, as well as targeted screening of childhood cancer survivors.[3] However, there is still much to learn regarding the interplay of patient specific factors, combined modality therapies and future lifestyle influences on chemotherapy related late effects.

Similarly, radiotherapy for children has evolved during the past two decades and advancements in delivery technologies have significant implications for late effects.[18] A rise in the utilization of intensity-modulated radiation therapy (IMRT), a type of photon therapy allowing improved dose conformation around the tumor and organs at risk, has led to concerns of increased secondary malignancy risk. These concerns relate to low-dose radiation exposure to a larger volume of uninvolved tissues with the increase in number of fields needed to deliver IMRT.[19] These exposures can be reduced through the use of proton radiotherapy, and with respect to adverse toxicities, early data suggest a potential benefit over photon radiotherapy,[20] when radiation is planned for structures with well-defined tolerances (cochlea, salivary glands, lung, bowel, kidneys, etc.).[21] For example, the shift to proton radiotherapy is anticipated to substantially reduce specific toxicities, such as hearing loss via reduced cochlear dose with conformal boost methods,[22] primary hypothyroidism and cardiac dysfunction due to the elimination of an exit dose from posteriorly directed CSI in both leukemia and brain tumor patients,[23,24] and neurocognitive decline by reducing exposure to healthy brain regions.[25] Organs known to be at high risk for morbidity from the combined effects of chemotherapy and radiation, such as the heart, may be more successfully spared with these novel techniques.[26,27] Future therapeutic trials should incorporate organ sparing and radiation dose reduction strategies in a disease and site specific manner.[28]

Like radiotherapy, surgery plays an important role in local control of many pediatric solid tumors, with long-term effects better appreciated as overall survival for childhood cancer has improved. Adverse effects of surgical local-control procedures on organ function, functional

status and quality of life have prompted evolution from radical resections to organ/tissue sparing surgeries and increased utilization of non-invasive strategies that leverage advances in diagnostic imaging technologies. For example, treating Wilms tumor in non-syndromic children with unilateral radical nephrectomy, without nephrotoxic chemotherapy or ionizing radiation, appears to result in low risk for significant long-term contralateral renal dysfunction.[29] In contrast, survivors with bilateral Wilms tumor or those with syndromic Wilms tumor (WAGR: Wilms tumor + aniridia + genitourinary malformation + mental retardation, and Denys-Drash syndrome) are at a substantially higher risk for long-term renal dysfunction.[30] Thus, the recommendation for nephron-sparing surgery for bilateral Wilms tumor balances dual goals of achieving local control and long-term survival while decreasing the risk of renal dysfunction. Likewise, surgical resection represents a common strategy for achieving local control of CNS tumors that often confers high risk for morbidity and premature mortality.[31] In patients with craniopharyngioma who are often treated with surgery alone, the location of the tumor inherently results in organ dysfunction (pan-hypopituitarism), functional impairment (visual deficits, strabismus and facial nerve palsy), and other chronic health conditions (obesity).[32] Recognition of late-effects associated with hypothalamic injury has resulted in recommendations for an experienced, multidisciplinary treatment approach including hypothalamus-sparing surgery with or without the addition of irradiation, preferably proton therapy, for unfavorably located tumors.[32]

Long-term effects of surgery on functional status are well appreciated, such as in survivors requiring chest wall resection in whom scoliosis is common and may lead to impaired pulmonary function and decreased exercise tolerance.[33,34] In survivors of extremity sarcomas, low scores on physical performance measures are reported, but not on mental or emotional measures.[35] In this population, limb-salvage surgery seems to offer better gait efficiency and return to normal living compared with above-knee amputation, but neither influence quality of life nor subjective well-being.[36]

Health outcomes research is continually expanding with the discovery and integration of novel therapies including new chemotherapeutic agents, targeted therapies, immunotherapy and new or improved hematopoietic stem cell transplant (HSCT) techniques. As an example, the use of tyrosine kinase inhibitors (TKIs) is increasing in pediatric leukemia management and we are beginning to learn the associated long-term effects, primarily from patients previously treated for chronic myelogenous leukemia (CML). Endocrinopathies associated with off-target action of TKIs include abnormal growth, impaired thyroid function and bone remodeling, as well as concerns for changes in pubertal development and glucose metabolism.[37] Additionally, as individuals are living longer after intensified multimodal therapy (e.g. survivors of high-risk neuroblastoma or those who received allogeneic HSCT as part of their therapy), continued follow-up to establish long-term outcomes is needed. As with all such research in pediatric cancer patients, challenges in determining therapeutic exposure risks and appropriate surveillance exist due to the variable nature of therapy and the latency to presentation of many late effects.

Patient-Specific Demographic Factors

Risk of adverse late health outcomes among childhood cancer survivors not only differs by primary cancer diagnosis and treatment exposure, but may vary according to patient-specific factors such as sex, race/ethnicity and age at diagnosis. Male survivors have higher absolute rates of late mortality (death ≥5 years from diagnosis), which is attributable to the lower life expectancy of males in the general population. Conversely, standardized mortality ratios, which compare the observed number of deaths in survivors to expected numbers based on general population rates and thus account for the sex difference in the general population, are higher in female survivors than males, suggesting that the long-term impact of cancer and its treatment may disproportionally increase risk for death in females.[38–40] In the Childhood Cancer Survivor Study, which examined 34,033 five year survivors of childhood cancer in North America, female survivors had higher standardized mortality ratios (SMRs) for all-cause mortality (females, SMR 21.2; males, SMR 10.0) as well as for mortality due to health-related causes (females, SMR 16.4; males, SMR 10.9), subsequent neoplasms (females, SMR 28.4; males, SMR 22.8), and cardiac (females, SMR 16.1; males, SMR 9.8) or pulmonary (females, SMR 20.4; males, SMR 15.9) causes.[38] Standardized all cause (females, SMR 11.7; males, SMR 7.9) and non-neoplastic cause (females, SMR 4.2; males, SMR 2.4) mortality was also higher for females in an analysis of 34,489 five year survivors in the British Childhood Cancer Survivor Study, although the same was not true for mortality due to subsequent neoplasms (females, SMR 5.7; males, SMR 6.8).[39] Female sex has also been associated with overall increased risk of chronic health conditions and impaired health status.[41–44] Certain studies have identified that females are particularly susceptible to anthracycline-mediated cardiomyopathy compared to males.[27,45,46] Additionally, female survivors are at a higher risk for subsequent malignant neoplasms, due largely to their increased risk of breast cancer.[47–50] Breast cancer risk is driven primarily by radiation exposure, but female survivors in CCSS not exposed to chest radiation also had increased risk compared to the general population, and alkylating agents and anthracyclines were associated with breast cancer risk in this group.[4,51] Despite varying results across studies, evidence supports sex-specific differences with higher risk among females compared to males for cognitive dysfunction after cranial radiation, obesity, hypothyroidism, and radiation-induced changes in pubertal timing.[52] In general, epidemiologic studies of late effects have not specifically focused on examining sex differences, but the higher risk among females has emerged from multivariable models that typically include factors such as cancer diagnosis and/or treatment exposures. The underlying mechanisms responsible for differences in risk of some late effects by sex are not well understood. Hormonal differences may play a role, but many children undergo treatment prior to puberty, when such differences would be expected to be minimal.

Few studies have comprehensively examined the role of race/ethnicity in late health outcomes among long-term survivors of childhood cancer. In the CCSS, non-Hispanic black survivors had higher all-cause mortality than non-Hispanic white survivors, although this disparity was abrogated after adjusting for socioeconomic status (SES).[53] No differences by race/ethnicity were observed in the overall cumulative incidence of severe, disabling, life-threatening or fatal chronic health conditions, but risk of cardiac conditions and stroke

was higher in non-Hispanic black survivors, and both non-Hispanic black and Hispanic survivors were more likely to report having diabetes compared to non-Hispanic white survivors.[53,54] These differences were largely attributable to underlying disparities in SES and cardiovascular risk factors. Importantly, studies have not identified a race/ethnicity-specific impact of treatment exposures on risk of late health effects in survivors, but future examinations of genetic susceptibility may reveal racial/ethnic differences in specific genetic variants that modify risk of late effects.

Because childhood is a period of critical growth and development, the age of cancer diagnosis and treatment can impact risk of subsequent treatment-related late effects. Risk of anthracycline-induced cardiotoxicity appears to be highest among children exposed in the first few years of life,[27,46,55] although further research is needed to definitively establish the independent contribution of age to cardiotoxicity risk.[56] Similarly, the adverse impact of cranial irradiation on cognitive function is particularly apparent among younger children in earlier stages of brain development.[57] Conversely, the adverse impact of cancer treatments on female reproductive function increases with older age at exposure due to the natural decline in oocyte number with age, leading to sterility at lower doses or premature ovarian failure at shorter intervals post-therapy.[58–61] Additionally, recent evidence suggests that the association between chest radiation and increased breast cancer risk is highest when exposure occurs near the time of menarche.[62,63] Although these patient-specific factors are not modifiable, understanding their impact informs the selection of frontline treatments for diseases in which more than one equally efficacious approach is available, as well as surveillance and prevention strategies among survivors. The evolution of therapy for Hodgkin lymphoma gives a prime example. Specifically, use of response-adapted therapy approaches, which allow for elimination of radiation therapy based on disease response without negatively impacting overall survival, limit therapeutic exposures and potential for late-effects, such as breast cancer risk in females.[64,65] Recent regimens have included lower cumulative doses of anthracyclines, alkylating agents and bleomycin compared to previous regimens in an attempt to reduce cardiovascular, pulmonary and fertility complications in addition to second malignant neoplasm rates.[64]

Genetics

Genetic variation can contribute to chronic disease risk among childhood cancer survivors in two ways. First, genetic predispositions known to confer moderate to high risk in the general population may contribute similarly to disease risk among survivors of childhood cancer.[66,67] For instance, a germline mutation in a cancer predisposition gene such as *TP53*, *BRCA1*, or *BRCA2*, which is known to greatly increase an individual's lifetime risk of developing cancer in the general population [68–70], is also a significant factor in determining subsequent cancer risk among childhood cancer survivors, independent of cancer therapy-related exposures.[71] Second, inherited genetic variation in pathways influencing treatment efficacy and toxicity may alter risk among survivors receiving certain treatment exposures.[72] For example, ovarian tumors with *BRCA* mutations have shown sensitivity to poly(ADP-ribosyl) polymperase (PARP) inhibitors related to impairment of DNA repair pathways, resulting in improved survival over those with *BRCA* negative tumors.[73] Genetic factors may also enhance risks for late onset toxicity as seen in patients

with hereditary retinoblastoma and germline *Rb-1* mutations, in whom radiotherapy confers a 3.1 fold increased risk of subsequent neoplasms over nonhereditary patients.[74]

One of the most well-studied chronic health conditions following cancer therapy among survivors is subsequent cancer.[49,75–77] Survivors of childhood cancer have a substantially higher risk of developing additional cancers than do individuals who have not previously had cancer during childhood. In addition, their risk of cancer is influenced by treatments received during childhood and by genetics.[78,79] Historically, an increased risk of hereditary cancer has been characterized by early age of cancer onset in the survivor or family members, a higher than expected number of cancers among family members and a personal history of multiple primary cancers or unusual clustering and presentations of cancer.[80] However, with advances in genetic sequencing technologies, we are now able to assess the impact of many germline variants on subsequent cancer risk by directly identifying these variants in an individual's genome. In a recent study, whole-genome sequencing of 2,988 childhood cancer survivors identified that 5.7% carried an underlying germline mutation in a known cancer predisposition gene that affected their risk of developing certain types of subsequent neoplasms in a complex manner depending on prior radiotherapy exposures.[71] Specifically, among survivors not treated with irradiation, mutation carriers had a significantly 5.6-fold increased risk of developing a subsequent neoplasm, the most common being basal cell carcinoma, meningioma, thyroid and breast cancer. Among mutation carriers, radiation therapy was significantly associated with a 2.3-fold increased risk of developing ≥2 subsequent neoplasms. This emerging data suggests that genetic risk in the childhood cancer survivor population as a whole may be significantly higher than previously understood and support the consideration of genetic counseling referral for all survivors to discuss the potential benefits and implications of testing after consultation and risk-assessment.[71]

Several studies have investigated the contribution of genetic variation to the risk of developing non-cancer chronic diseases among childhood cancer survivors. Many of these studies have adopted a candidate gene approach, selecting candidates based on known drug metabolism pathways or the underlying pathobiology of the chronic disease. Among the most extensively studied long-term outcomes to date is anthracycline-induced cardiotoxicity. Genes in which polymorphisms have been associated with cardiomyopathy and/or congestive heart failure include, but are not limited to *SLC2A3*, *ABCB1*, *ABCB4*, and *ABCC1*, which are involved in drug transport[81]; *CBR3*, which is associated with the two-electron reduction of anthracyclines, a main route of anthracycline metabolism[82,83]; *CELF4*, a regulator of alternate protein splicing, including cardiac troponin[84]; and *HAS3* and *NCF4*, both of which are implicated in defense against reactive oxygen species.[85–87] Similarly, studies among ALL survivors have identified that polymorphisms in genes likely to affect the action of anti-leukemia medications, such as *VDR* and *TYMS*, are associated with osteonecrosis,[88] while *CRHR1* polymorphisms alter the risk of bone density deficits.[89] Although profiling of relevant genetic variation may characterize the risk of a specific disease and identify sub-populations of survivors at high risk, most reported gene-disease associations among childhood cancer survivors have not been extensively replicated, and consequently, their utility has not yet been established.

Interaction of Cancer Therapy with Premorbid and Comorbid Conditions

The implications of childhood cancer therapy for adult health are substantial. Investigators have reported a high prevalence of chronic illness among childhood cancer survivors and, by applying a modification of the National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE), have described the severity of these late outcomes.[90] Age-related health conditions appear earlier and with greater severity than might otherwise be expected. Approximately two-thirds of survivors in the CCSS reported at least one chronic health condition at a mean age of 26.6 years (range: 18.0–48.0), and the adjusted relative risk of a chronic condition in survivors was 3.3 (95% CI, 3.0–3.5) compared with siblings.[43] In a large Nordic cohort, childhood cancer survivors were found to have a 1.8-fold risk of hospitalization compared to population based controls, with younger survivors having a higher relative risk than those in later decades of life.[91] Subclinical disease can be significant, but is only identified if childhood cancer survivors are systematically screened. In a single-center study of 1,362 five-year survivors, 1,015 (75%) survivors had at least one chronic health condition.[41] Participants in the St. Jude Lifetime (SJLIFE) cohort were systematically screened per the COG Long-Term Follow-Up Guidelines, and were found to have a particularly high prevalence of pulmonary, auditory, endocrine, cardiac, and neurocognitive abnormalities. The estimated cumulative prevalence by age 45 years was 95.5% (95% CI 94.8–98.6%) for any chronic condition and 80.5% (95% CI 73.0–86.6%) for a serious/disabling or life-threatening condition.[5] However, childhood cancer survivors typically experience more than one chronic health condition. Among CCSS participants, 24-year-old survivors experienced the same cumulative incidence of severe, disabling, life-threatening or fatal health conditions as 50-year-old siblings (19.6%). At age 50 or older, 22.5% of survivors reported two or more CTCAE grade 3–5 conditions compared to 4.3% of siblings.[4] The burden of disease among this young adult population can be significant. Using the cumulative burden, a novel measurement of disease burden that incorporates multiple health conditions and recurrent events into a single metric, Bhakta *et al.* estimated that by 50 years of age, survivors in the SJLIFE cohort would have, on average, 17.1 chronic health conditions, more than four of which are expected to be severe/disabling or life-threatening, representing a two-fold greater health burden compared to an age- and sex-matched community control population.[28]

Traditional risks to health, such as obesity, diabetes mellitus, and hypertension, which may occur on a background of advancing age, genetic predisposition, or suboptimal lifestyle behaviors, may have more than additive effects on cancer-related complications and contribute to worse long-term health outcomes. In a CCSS report, the risk of major cardiac events among survivors who had been exposed to anthracycline and/or chest-directed radiation was potentiated in a more than additive way by modifiable cardiovascular risk factors, most notably hypertension.[92] Smoking and alcohol consumption were independently associated with severe bone mineral density deficits and frailty,[93] a phenotype shown to be predictive of mortality in childhood cancer survivors.[94] Neurocognitive and emotional problems may also influence health behaviors and adherence to screening.[95] Poor health-related quality of life and the frequent need for psychotropic drugs (antidepressants, analgesics) may further complicate care.[96] Consideration of chronic conditions, patient

specific factors, health behaviors and early interventions could modify the trajectory of anticipated morbidity and mortality experienced by childhood cancer survivors, as demonstrated in this example of cardiomyopathy (Figure 2).

Undiagnosed or untreated chronic conditions may contribute to worse long-term health outcomes in an already vulnerable population.[5] For example, only 31% of childhood cancer survivors with premature ovarian insufficiency (POI) reported receiving hormone replacement therapy in SJLIFE while POI was found to be independently associated with poor bone mineral density and frailty in the same study.[98] Furthermore, data remain limited regarding the safety and long-term benefit of certain interventions such as growth hormone replacement in adults[99] or sex hormone replacement in women experiencing premature menopause.[63,98] While initiation of hormone replacement therapy (HRT) for females in the general population with POI is recommended, with guidance to continue until the age of natural menopause,[100] there is not a clear consensus for HRT in childhood cancer survivors. Evidence based guidelines provide direction on surveillance for POI in high risk female childhood cancer survivors,[101] but decisions to initiate or continue HRT are considered on an individual basis. The modification of breast cancer risk by hypogonadism and HRT, particularly in those with a history of chest irradiation, has been of particular interest. Recent studies suggest that in hypogonadal individuals, HRT with combined estrogen and progesterone has no, or only moderately, increased risk of breast cancer compared to those not receiving HRT, and nevertheless, remains lower than the risk in non-hypogonadal female survivors who also received chest irradiation.[63,102] Further study is needed to investigate the risks and benefits of HRT in this population, in particular, regarding breast cancer risk, as well as cardiovascular and bone mineral density outcomes. Improving general health outcomes by intervening on modifiable risk factors remains an area of active research.

Aging and Frailty

A proportion of childhood cancer survivors are at risk for pre-frailty or frailty, states of reduced physiologic reserve, characterized, respectively, by the presence of two and three or more of the following impairments: 1) low energy expenditure, 2) low lean muscle mass, 3) fatigue, 4) weakness and 5) slow walking speed.[103] This phenotype is most often described among older adults, suggesting that childhood cancer survivors may be at risk for accelerated aging. In the SJLIFE cohort, at a mean age of 33.6±8.1 years, pre-frailty was present among 22.2% and frailty among 7.9% of adult survivors of childhood cancer, and was associated with a 2.2-fold (95% CI 1.2–4.2) increased risk for new onset chronic disease and a 2.6-fold (95% CI 1.5–2.8) increased risk for death.[94] These data are similar to data from the Cardiovascular Health Study cohort of older adults, ranging in age from 65–101 years of age, where pre-frailty was reported among 15.0%, and frailty among 7.2% of participants.[103] This phenotype appears early during the course of childhood cancer therapy. Children with newly diagnosed cancer present with diminished exercise capacity, weakness and low lean muscle mass.[105] After cancer therapy, sub-optimal recovery is apparent, as adolescent survivors also have been shown to have lower exercise capacity and reduced muscle strength compared to peers.[106,107] This early impairment may perpetuate a sedentary lifestyle that contributes to failed recovery of normal physiologic reserve. Studies in large

cohorts of childhood cancer survivors indicate that they are less physically active than their siblings or age and sex-matched controls.[108–110]

The prevalence of frailty among childhood cancer survivors increases with age and is higher among females. Exposure to cranial, abdominal or pelvic radiation, the development of endocrine dysfunction, and smoking are associated with frailty among adult survivors of childhood cancer.[93,99,94] However, those without these exposures are also at risk. It is possible that the disease itself, or exposure to DNA damaging agents, results in loss of existing tissue integrity and underlying cellular function, subsequently impairing the abilities of the cardiopulmonary, musculoskeletal and neurosensory systems to support and respond to movement. Preliminary research among small groups of survivors suggests that telomere attrition, chronic inflammation, and early cellular senescence are potential mechanisms to explain these findings. Arittfin *et al.* reported shorter leukocyte telomere length, and increased plasma levels of C-reactive protein and interleukins 2, 10 and 17a among adult (age range 18–35 years) survivors of childhood ALL who were five or more years from diagnosis when compared to age- and sex-matched controls.[111] Marcoux *et al.* reported increased expression of $p16^{INK4a}$, a marker of cellular senescence, in scalp when compared to buttocks biopsies of ten ALL survivors previously exposed to cranial irradiation, suggesting a differential effect in cells exposed to radiation.[112] Research also suggests that mitochondrial dysfunction is associated with chemotherapy exposure, and may explain the persistent loss of muscle mass observed in childhood cancer survivors.

Interventions specifically designed to prevent or remediate frail health among childhood cancer survivors have not been tested. Additional research to elucidate the pathobiology of the frailty phenotype should provide biological or molecular targets for intervention. While this work is ongoing, exercise interventions that work in other populations to improve low muscle mass, muscle strength and exercise capacity may benefit those childhood cancer survivors with reduced physiologic reserve.

Health Behaviors

Health behaviors contribute to the expression of late effects in survivors of childhood cancer. Reducing risky and promoting protective health behaviors in this population may help ameliorate adverse health outcomes such as secondary cancers and both cancer and non-cancer related morbidity and mortality. Health behaviors that contribute to late effects of cancer therapy include those related to tobacco, alcohol and illicit drug use, physical inactivity and poor diet, excess sun exposure and risky sexual behaviors (e.g. exposure to HPV). Table 2 describes recent studies that indicate the prevalence of these health behaviors as well as associated risk factors.[95,109,110,113–125] Overall, survivors tend to exhibit risky behaviors at rates similar to or just less than their siblings, non-cancer controls, and the general population. However, due to vulnerability as a function of disease and/or treatment, survivors may be more sensitive to these risky behaviors and they should be limited as much as possible.

As is seen in the general population, engaging in risky or suboptimal health behaviors has implications for the overall health of survivors. For instance, survivors with better

diet quality have lower adiposity,[126,127] waist circumference[127] and BMI[127]; whereas those with poor diet have an excess risk of conditions associated with the metabolic syndrome.[120,128] Similarly, compared to inactive survivors, those with higher rates of physical activity are more likely to have lower percent fat mass, abdominal visceral fat,[129] and waist circumferences.[130] Survivors with declining physical activity report more chronic musculoskeletal conditions.[110] Regarding use of illicit substances in the survivor population, marijuana and tobacco use have been linked to risk of pulmonary complications while cocaine and methamphetamine abuse have been associated with cardiac problems.[131] While further research regarding marijuana use is needed, particularly as both recreational and legalized use of various forms have evolved, inhaled marijuana places survivors at risk for respiratory problems and can exacerbate pre-existing pulmonary late effects. In the general population, marijuana smoking is associated with increased forced vital capacity (FVC), in contrast to the reduction seen in tobacco smokers, and has been associated with symptoms of COPD and chronic bronchitis. Additionally, some studies suggest increases in bullous lung disease and hyperinflation, while evidence regarding lung cancer risk remain inconclusive.[132,133] Overall, the findings of these studies are limited, in part due to potential confounding from frequent concurrent tobacco use, but demonstrate a need for further research in both the general and survivor population.

Low educational attainment (i.e., less than high school education) and lower household income among survivors have been associated with risky health behaviors, including physical inactivity, smoking, and drinking. As seen in the general population, low educational attainment and annual household income <$20,000 were associated with an increased risk of non-cancer related mortality among survivors.[134] These behaviors subsequently place survivors at risk for the development of chronic disease[135] and death.[134]

Several emerging health behaviors need more investigation, such as opioid and medical marijuana use, to understand the prevalence and risk factors in this population. Moreover, there is a need for interventions targeting health behavior change. Future work should draw upon previous findings that have shown efficacy in this population including use of biochemical verification in tobacco interventions,[136] assisting with decision-making related to substance use,[137] and using websites,[138] videogames and other electronic formats to encourage healthy eating. Designing physical activity interventions that utilize group exercise or increase self-efficacy,[139] as well as promoting ecological/environmental interventions such as active transportation[140] and adventure-based training[141,142] are areas to explore. Interventions that target alcohol use, sunscreen behavior and risky sexual behavior are limited and require further investigation.

Socioeconomic and Psychosocial Factors

Socioeconomic Factors and Access to Care

Numerous studies have documented that adult survivors of childhood cancer are at-risk for reduced educational attainment,[143–146] increased financial burden,[147] underemployment,[148,149] dependent living status,[150] and limited health insurance coverage.[151] Consistent with observations from the general population, SES, specifically

low educational attainment and household income, is directly associated with an increased risk of non-cancer related mortality among survivors.[134]

Lack of health insurance is a significant barrier to accessing medical care in the United States for adults with chronic conditions.[152] Adult survivors of childhood cancer potentially face additional barriers to obtaining adequate health insurance coverage compared to the general population.[148,153] These factors challenge the delivery of adequate care to survivors and may delay the diagnosis of chronic health conditions.[5] Among childhood cancer survivors, decreased access to health care has been associated with reduced utilization of survivor-focused and general preventative health care.[154] In a report from the CCSS cohort, nearly 30% of uninsured survivors had received no medical care in the prior two years compared with 10% of insured survivors.[155] Importantly, general and survivor-focused health care is critical for prevention and treatment of chronic diseases, a major contributor to late mortality in adult survivors of childhood cancer.[156] Survivors of childhood cancer in other countries may face different health insurance challenges. A study of the Norwegian population demonstrated that childhood cancer survivors had a significant increase in utilization of national insurance benefits, specifically for added expenses from disability, compared to the general population.[157]

Psychological Distress

Adult survivors of childhood cancer are at-risk for the development of psychological symptoms (i.e., depression and anxiety) compared with sibling controls.[158] In long-term survivors of childhood cancer, symptoms of psychological distress, particularly suicidal ideation, have been associated with increased risk of all-cause mortality.[159] Research has shown that factors such as worry, concern, and the extent to which survivors believe they have control over their health (i.e. locus of control) predict pediatric cancer survivors' self-reported participation in medical surveillance[160] – potentially modifying the likelihood and severity of late effects. Recent research has demonstrated that survivors who develop cardiovascular, endocrine, and/or pulmonary conditions resulting from cancer-directed therapies in childhood are at risk for developing emotional distress (e.g., symptoms of depression and anxiety).[161] Further investigations are needed to establish the temporal order between chronic health conditions and psychological distress among survivors as well as to determine the effect of interventions designed to target these modifiable risk factors.

Parental distress is predictive of child distress, during both active cancer treatment[162] and survivorship.[163] Similarly, family factors, such as cohesion and expressiveness, have been shown to predict child distress during treatment.[162] Research from the general population indicates that adverse childhood experiences, including family dysfunction and parental mental illness, significantly increase the risk of chronic health conditions in adulthood.[164,165] The potential impact of similar factors such as parental distress and family environment on the morbidity and mortality of aging survivors has not yet been studied.

Chronic Pain, Sleep and Neurocognition

Over half of survivors of childhood cancer report the presence of pain in adulthood. Pain has been shown to impair survivors' quality of life,[166] and to predict persistent psychological

distress in survivors over time.[167] Although the presence of *chronic* pain (i.e. persistent or recurrent pain lasting >3 months) has not been examined among adult survivors of childhood cancer, in the general population chronic pain affects 10–11% of adults,[168] is associated with depression,[169] anxiety,[170] decreased activity,[171] and increased disability.[172] Pain has also been associated with sleep problems and subsequent fatigue in the general population.[173] During adulthood, long-term survivors of childhood cancer frequently report poor sleep quality and fatigue, though at levels that are not substantially different than siblings.[174] Sleep disturbance and fatigue in survivors has been independently associated with increased risk for neurocognitive impairment, beyond the risk associated with cranial irradiation and neurotoxic chemotherapies.[175] Fatigue has also been strongly associated with reduced quality of life.[166] Recent research in adolescent survivors of childhood cancer has demonstrated that sleep disturbance is also associated with increased biomarkers of systemic inflammation,[176] which may impact future risk for chronic health conditions.

Survivors who receive cranial irradiation,[177,178] are exposed to high dose systemic or intrathecal methotrexate,[179] or experience treatment-related cardiopulmonary and/or endocrine disease are at increased risk for neurocognitive impairment.[180] Social attainment and future health behaviors are negatively impacted by this impairment. Survivors who develop neurocognitive problems during adolescence are more likely to engage in risky health behaviors and less likely to engage in health care utilization as adults.[181] Long-term survivors of childhood cancer who develop neurocognitive problems are also less likely to graduate college,[182] work full-time,[148] and live independently.[150]

Screening Guidelines and Delivery of Care

Survivorship Guidelines

The many potential late effects of cancer therapy have necessitated a systematic approach to early detection and intervention. To address this need, guidelines have been developed by several leading childhood cancer organizations.[183] As guidelines were developed independently by multiple international groups, variations exist in their recommendations regarding patient risk groups and surveillance testing and intervals, due to variation in capacity to implement guidelines. Currently, the International Late Effects of Childhood Cancer Guideline Harmonization Group is working to establish integrated clinical practice guidelines for surveillance of late effects in childhood cancer survivors.[183]

In North America, the Children’s Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers represent the primary survivorship resource for healthcare providers.[184,185] The COG guidelines pair evidence linking therapeutic exposures to observed late effects and provide consensus-based screening and management recommendations. Although this strategy can improve the detection of health conditions,[5,186] the cost-effectiveness of screening and management and the ultimate impact on clinical outcomes remains uncertain. Two studies on the cost-effectiveness of the COG’s cardiomyopathy screening recommendations provided evidence that although existing screening strategies for cardiomyopathy were cost-effective in survivors at higher risk, optimal cost-efficacy could be achieved through reduced screening frequency from every 1 to 5 years to every 2 to 10 years depending on the risk group which maintained 80%

of the health benefits of screening.[187,188] However, these studies highlight a need for future research seeking to optimize cost-effective implementation of survivorship guidelines and their impact on clinical outcomes.

In 2010, the International Late Effects of Childhood Cancer Guidelines Harmonization Group was established to address the significant variation among existing guidelines.[183] Applying rigorous guideline development methodology, this collaboration has resulted in the completion of four uniform surveillance guidelines (cardiomyopathy, breast cancer, and both male and female gonadal dysfunction), with several others in progress.[56,101,189,190] This undertaking will establish an acceptable and generalizable set of surveillance recommendations directing optimal strategies for global delivery of survivorship care.

Models of Care and the Survivorship Care Plans

Different survivorship care models have been utilized across many clinical settings[191]; however, little evidence exists to prioritize the use of any one approach.[192,193] All care models essentially seek to: 1) monitor for treatment-related late effects, 2) educate and engage patients and providers, and 3) provide appropriate management of cancer-related medical issues (Figure 3).[194,195] The success of a given approach is largely dependent upon resource availability; therefore, the preferred model is one that can be effectively supported in a given clinical setting.

In high-income countries, many children are diagnosed with and treated for cancer at comprehensive cancer centers, where institutional commitments may be leveraged to support resource-intense multidisciplinary care models, typically involving a pediatric oncologist, internist, appropriate sub-specialty providers for individual patient needs and behavioral clinicians such as a social worker and psychologist. This approach capitalizes on availability of specialty services to provide centrally coordinated and administered comprehensive care. While some authors suggest that multidisciplinary clinics such as these are optimal,[191] these centers are often specialized to care for children and may not be best suited to provide quality, cost-effective care to adult survivors of childhood cancer.[196] Conversely, regions with fewer resources may choose to utilize consult-based approaches, in which assessments are performed by specialists and care subsequently transferred to the primary care team.[197] Many have advocated for a more intermediate approach, such as the shared care model, which involves initial coordination of care by the cancer center, with carefully planned transition of care to primary providers who then have access to ongoing support from the cancer center.[198] This approach requires excellent communication systems, which can be challenging in the current healthcare structure. An alternative approach, the patient-centered medical home, has not been widely utilized in cancer survivors but is often implemented to provide community-based care for children with other medically complex conditions (e.g. diabetes) with the goal of accessible, coordinated and patient-centered care. This strategy could facilitate collaborative care between primary providers and survivorship specialists through routine specialist visits to the patient-centered medical home, providing an alternative shared care approach to community-based care for childhood cancer survivors.[199,200]

For aging survivors, delivery of care is complicated by the need to transition not only from treatment to survivorship and/or primary care, but also from pediatric to adult providers. The importance of effective transition of care has been recognized and is under active investigation in other pediatric chronic conditions, such as sickle cell and congenital heart disease.[201,202] Within general pediatrics, some have suggested that beginning the process early, engaging the child in medical decision-making, and maintaining health insurance are important factors in this transition.[203] Unique to childhood cancer survivors is that this transition often occurs during the hiatus between active cancer treatment and the onset of late-effects, raising concern that survivors may fail to recognize the importance of ongoing follow-up care. While data to address these concerns are lacking, they underscore a belief in the importance of empowering survivors through ongoing cancer treatment-related history and associated health risk education, emphasizing the value of continued follow-up care.[195] Additionally, guidelines in existence tend to emphasize medical outcomes rather than psychosocial or socioeconomic factors impacting survivor care and transition. The COG Long-Term Follow-Up Guidelines briefly address psychosocial outcomes,[184] such as education and employment deficits, social withdrawal and dependent living, mental health disorders, and risky health behaviors, however, similar to guidelines from international groups,[204] there are challenges in meeting these needs, as well as medical needs, including specific system (e.g. health insurance, access to mental health and rehabilitation services), provider (e.g. setting of practice, training, perceptions of care) and survivor (e.g. self-efficacy, health literacy and knowledge) barriers (Figure 4).

Regardless of the chosen model of survivorship and transition care delivery, leading organizations have recognized the growing need to optimize the systematic delivery of evidence-based recommendations to providers and cancer survivors of all ages. The use of personalized treatment summaries and survivorship care plans, which document possible complications of cancer-treatment, signs of recurrence, and recommended follow-up, is supported by many organizations.[192] These documents are intended to enhance adherence, improve communication between oncology and primary care providers, and ultimately improve delivery of care. However, their effectiveness remains only anecdotal, and existing studies raise concerns about: 1) the feasibility of providing these documents to both patients and providers and 2) which components of the document are essential for inclusion.[155,197,205,206]

Conclusions

Comprehensive, risk-based care of the childhood cancer survivor is a complex and multi-faceted undertaking. It requires the cooperation of clinicians and patients as well as the care network responsible for these patients. Although we have identified many contributors to morbidity and mortality in this population, ongoing research is needed to assess the efficacy of interventions, to identify possible targets for mitigation of late effects, and to develop effective screening strategies to assist with early diagnosis and prevention. The heterogeneity of the childhood cancer survivor population, not only in cancer type and treatment factors, but also demographics, genetics, health behaviors and socioeconomic factors highlights the importance of a patient-specific, risk-based approach to care. New challenges and opportunities for research will emerge as the treatment of pediatric

cancer continues to introduce novel agents, therapeutic reductions and alternate treatment approaches whose effects will be realized only in the next generation of childhood cancer survivors.

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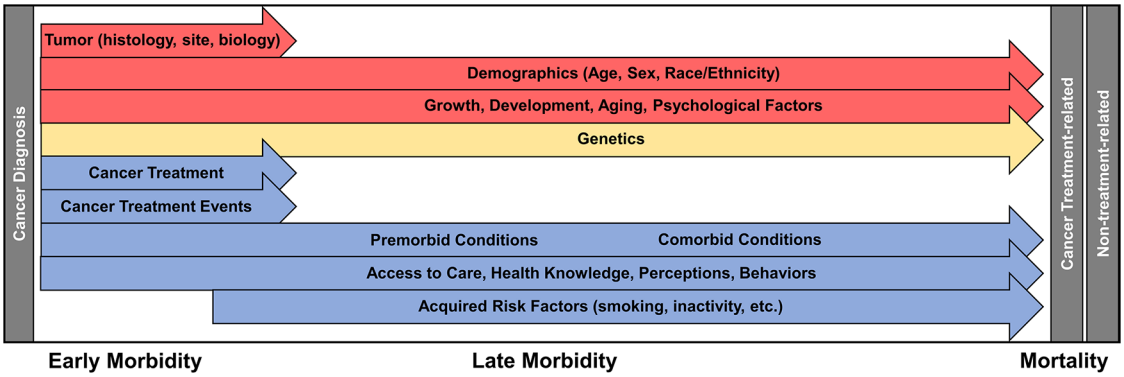

Figure 1.

Factors influencing morbidity and mortality of the childhood cancer survivor. Each arrow demonstrates a different factor affecting morbidity and mortality which exert their effect along a continuum of care. Note that all effectors can begin exerting influence on morbidity during the period of cancer-directed therapy. Factors are separated into those that cannot be modified (red), those for which future interventions are plausible (yellow) and those for which there are known targets for interventions or areas where therapy and surveillance have already been modified (blue).

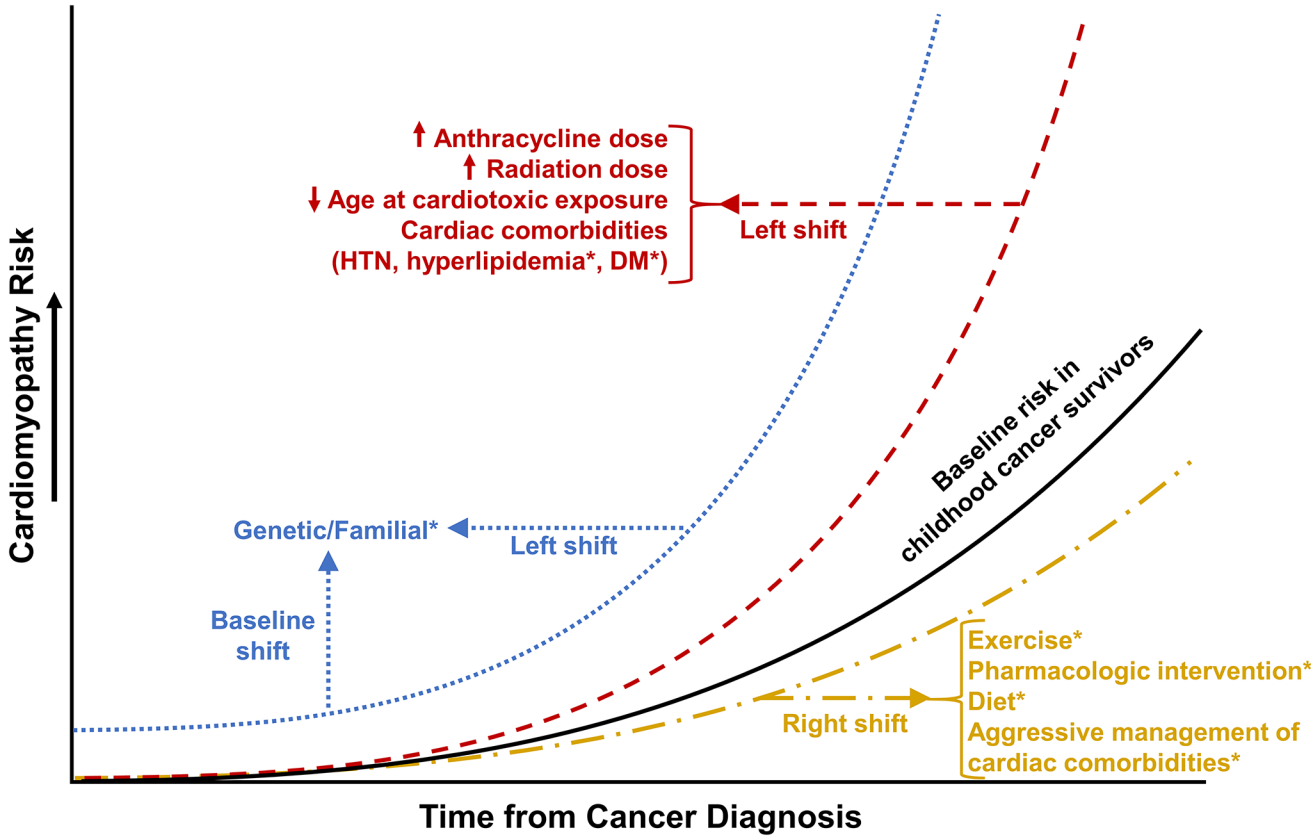

Figure 2.

Conceptual schematic of cardiomyopathy risk and modifiers in childhood cancer survivors. Factors designated by an *asterisk* are under active investigation (knowledge gaps). HTN hypertension, DM diabetes mellitus. Reproduced with permission from Springer Publishing Company. Ehrhardt, MJ, Fulbright JM, Armenian SH. Cardiomyopathy in childhood cancer survivors: lessons from the past and challenges for the future. *Curr Oncol Rep*, 2016. 18(4): 22.

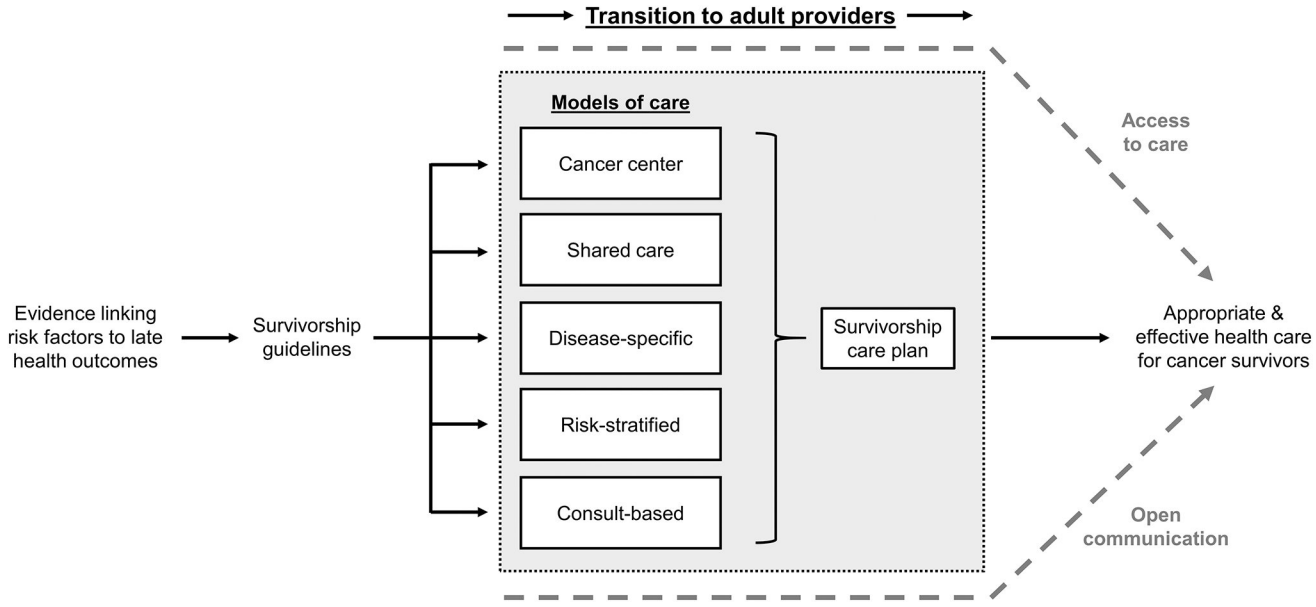

Figure 3.

The continuum of childhood cancer survivor care delivery.

"Cancer center" model: care provided within the cancer center, either by the primary oncology or dedicated survivorship teams. "Shared-care" model: care initially provided in the cancer center, with later transfer to community providers with ongoing communication and specialty support from the cancer center. "Disease-specific" model: cancer center-based survivorship clinics designed to specifically address the needs of a particular at-risk population (e.g. central nervous system tumor survivors). "Risk-stratified" model: stratified care is provided based on risk categorization, with survivors at higher risk of late effects being seen at more comprehensive centers and those with lower risk cared for in the community. "Consult-based" model: care administered in the community care provider's office (i.e. the general pediatric or adult medicine provider) with consultation for specific late effects obtained as needed without ongoing specialty involvement unless clinically indicated.

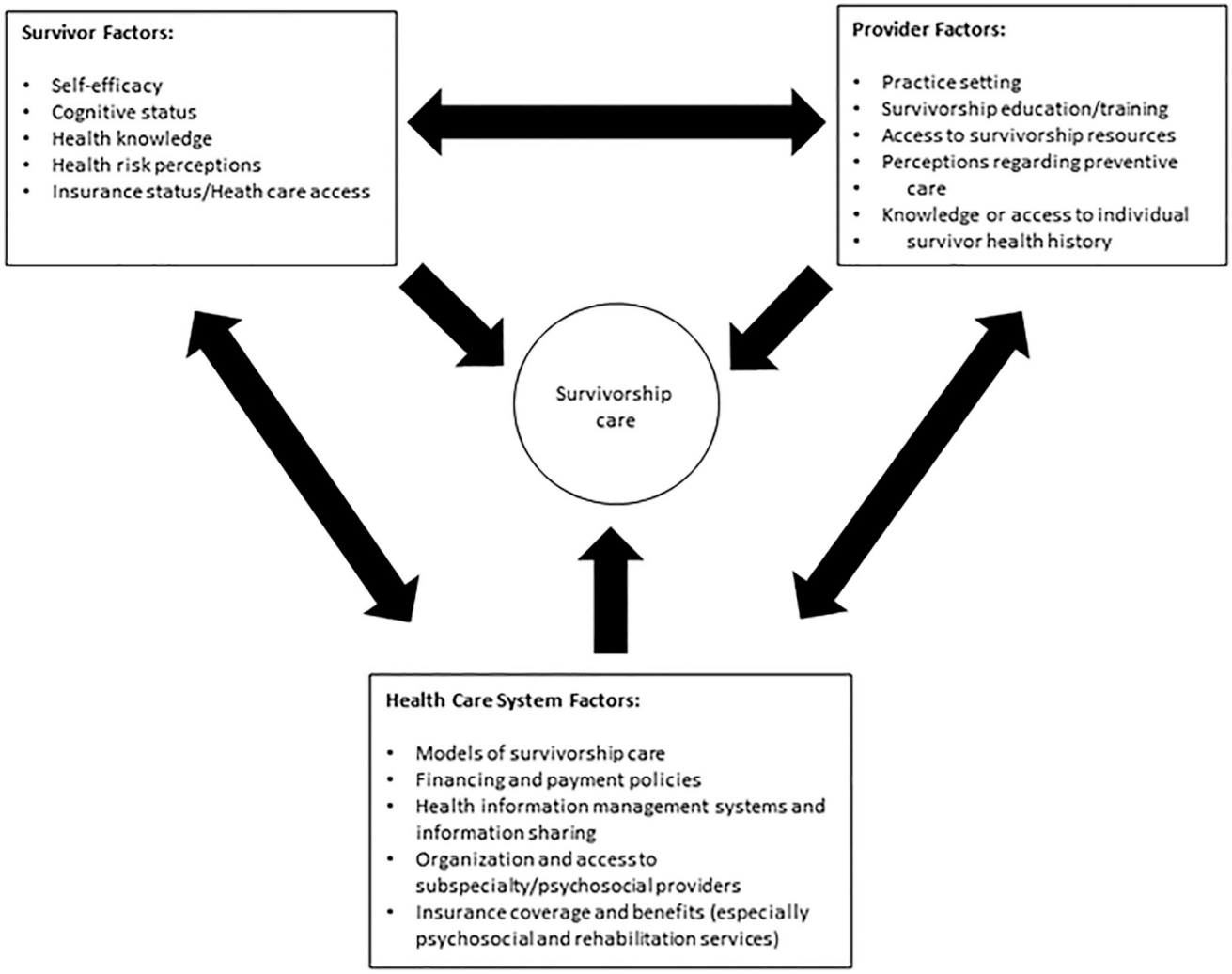

Figure 4.

Survivor, provider and health care system factors that may act as barriers to survivorship care. The arrows demonstrate that factors in one domain may influence other domains. Directed interventions should be developed within the setting and context of care system.

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Table 1.

Organ System Dysfunction Associated with Pediatric Cancer Therapy

Organ System	**Specific Late Effect**	**Therapeutic Exposure**	**Modifying Factors**
Auditory	Sensorineural hearing loss Tinnitus Vertigo	Cisplatin Carboplatin Radiation impacting the ear	Younger age (< 4 years) at treatment at higher risk
	Tympanosclerosis Otosclerosis Eustachian tube dysfunction Conductive hearing loss	Radiation impacting the ear	Younger age at treatment at higher risk
Cardiac	Cardiomyopathy Arrhythmias Subclinical left ventricular dysfunction Valvular Disease Pericardial Disease	Anthracyclines (daunorubicin, doxorubicin, idarubicin, epirubicin) Radiation impacting the heart	Younger age (< 5 years) at treatment at higher risk for all except pericardial disease Females at higher risk of cardiomyopathy and valvular disease Family history Genetic factors (variants effecting anthracycline metabolism) Health behaviors (diet, exercise, alcohol, smoking) Cardiovascular risk factors (hypertension, obesity, diabetes) Non-Hispanic Black race increases risk
Vascular	Coronary artery disease including myocardial infarction Carotid or subclavian artery disease Stroke Moyamoya Occlusive cerebral vasculopathy	Radiation impacting cardiovascular or cerebrovascular structures	History of Down syndrome, sickle cell disease or neurofibromatosis Female gender protective for myocardial infarction Non-Hispanic Black race increases risk Family history Health behaviors (diet, exercise, alcohol, smoking) Cardiovascular risk factors (hypertension, obesity, diabetes)
Organ System	**Specific Late Effect**	**Predisposing Therapy**	**Modifying Factors**
Endocrine/ Metabolic	Overweight/obesity	Radiation impacting the brain (≥18 Gy) or TBI Abdominal radiation Hypothalamic injury from tumor growth or surgery	Younger age (<10 years) at treatment Girls at higher risk Health behaviors (diet, exercise) Mental health (certain antidepressant use)
	Metabolic syndrome Diabetes mellitus	Radiation impacting the brain (≥18 Gy) or TBI Abdominal radiation Cisplatin (with CRT) Glucocorticoids HSCT	Younger age (< 4 years) at treatment Minority populations at higher risk Health behaviors (diet, exercise)
	Primary Hypothyroidism	Radiation impacting thyroid gland HSCT (due to antibody transfer)	Younger age at irradiation at higher risk Girls at higher risk
	Hypothalamic/pituitary dysfunction (growth hormone deficiency, central precocious puberty, LH/FSH deficiency, TSH deficiency, ACTH deficiency)	Tumors located within or near the hypothalamus Radiation impacting hypothalamic-pituitary axis including TBI (dose dependent response with growth hormone being most sensitive Tyrosine Kinase Inhibitors	Radiation-related deficiencies may appear at lower doses with longer follow-up
	Decreased bone mineral density	Methotrexate Glucocorticoids TBI	Health behaviors (weight bearing exercise, smoking)

	Secondary Thyroid Cancer	Irradiation of the neck	Background risk increased in patients with genetic predisposition (DICER 1, PTEN)
Hepatic	Chronic hepatitis C	Blood product transfusion prior to donor screening implemented in 1992	Health behaviors (IV drug abuse)
	Hepatic dysfunction Hepatic steatosis/cirrhosis	Thioguanine Methotrexate Mercaptopurine Busulfan History of treatment related veno-occlusive disease	History of chronic hepatitis Health behaviors (alcohol use) Obesity Diabetes mellitus Concurrent statin therapy
Immune/spleen	Asplenia Hyposplenia	Radiation (≥ 40 Gy) impacting spleen Splenectomy	History of chronic graft versus host disease
Musculoskeletal	Low lean muscle mass/weakness Decreased exercise capacity Frailty or accelerated aging	Possible effects of: Corticosteroids Doxorubicin Radiation therapy impacting brain, abdomen or pelvis Lower extremity amputation	Female sex Comorbid conditions (endocrine dysfunction) Lifestyle (physical activity) Health Behaviors (smoking)
	Scoliosis	Radiation therapy impacting chest wall or thoracic spine Chest wall resection	
Nervous system	Peripheral sensory or motor Neuropathy	Cisplatin Vinca alkaloids	History of Charcot-Marie-Tooth disease
	Clinical leukoencephalopathy (spasticity, ataxia, dysarthria, dysphagia) Hemiparesis Seizures	Methotrexate (high dose intravenous or intrathecal) Cytarabine (high dose intravenous or intrathecal) Radiation impacting the brain	Younger age at treatment at higher risk
	Neurocognitive deficits	Methotrexate (high dose intravenous or intrathecal) Radiation impacting the brain Corticosteroids in patients not receiving radiation	Younger age at treatment at higher risk Female sex at higher risk Psychologic and socioeconomic factors
Pulmonary	Interstitial pneumonitis Pulmonary fibrosis Restrictive lung disease Obstructive lung disease	Bleomycin Busulfan Carmustine (BCNU) Lomustine (CCNU) Radiation impacting the lungs	Younger age at treatment at higher risk Health behaviors (smoking) Occupational exposures
Renal	Glomerular toxicity Tubular toxicity (renal tubular acidosis, Fanconi's syndrome, hypophosphatemic rickets)	Cisplatin Carboplatin Ifosfamide Radiation impacting the kidney Surgical resection of kidney	Mononephric Comorbid conditions (HTN, diabetes)
Urinary Tract - Bladder	Hemorrhagic cystitis Bladder fibrosis Dysfunctional voiding Vesicoureteral reflux Hydronephrosis	Cyclophosphamide Ifosfamide Radiation impacting the bladder Surgery impacting the bladder/bladder outlet	No predisposing host factors
Reproductive system	Infertility Reduced ovarian reserve	Cyclophosphamide or other alkylating therapy Heavy Metals Radiation therapy impacting gonads	Risk increases with age at exposure in females.

	Sexual Dysfunction	Pelvic floor surgery – female Bladder/prostate surgery – males Surgery affecting spinal cord	Health behaviors (alcohol, illicit drug use) Comorbid endocrine dysfunction Mental health disorders
Vision	Cataracts	Busulfan Radiation impacting the eye	

CRT = cranial radiation therapy; HSCT = Hematopoietic stem cell transplant

Table 2.

Selected studies examining prevalence and risk factors regarding health behaviors in childhood cancer survivors.

Health Behavior	Source	Survivor Population	Comparison Group	Findings	Risk Factors Identified in Survivors*
Tobacco Use	Gibson et al, 2015[102]	N=9397 53% male Age at diagnosis: 0–20 years Age at evaluation: Mean 28 years	N=4023 siblings and general population from the NHIS	19% CCS were smokers compared to 24% of siblings and 29% in the general population at baseline; smoking in CCS dropped to 16% at follow-up	Psychological distress and heavy drinking=more likely to smoke; cranial radiation and psychological distress=less likely to quit smoking
	Emmons et al, 2002[103]	N=9709 54% male Age at diagnosis: <21 years Age at evaluation: Median 26 years	None	28% were ever smokers; 17% were current smokers	Lower household income; lower educational attainment; older age at cancer diagnosis
Alcohol Use	Rebholz et al, 2012[94]	N=1049 53.3% male Age at diagnosis: 0 to 10+ years Age at evaluation: 15–40 years	N=5207 population controls in the Swiss Health Survey	CCS consumed alcohol more frequently than controls (OR=1.7; 95% CI=1.3–2.1) and engaged in binge drinking more frequently (OR 2.9; 95% CI=2.3–3.8)	Male sex; higher educational attainment; geographic location
	Lown et al, 2008[105]	N=10398 54% male Age at diagnosis:<21 years Age at evaluation: 18–48 years	N=3034 siblings; N=4774 participants National Alcohol Survey	Survivors slightly more likely to be current drinker compared to siblings; less likely to be risky or heavy drinkers	Current age 18–21 years old; male; lower educational attainment; young age at drinking initiation; distress
Illicit Drug Use	Milam et al, 2015[106]	N=193 50.3% male Age at diagnosis: Median 12.1 years Age at evaluation: Median 19.9 years	None	14% reported current marijuana use	Male sex; depressive symptoms; higher socioeconomic status
	Klosky et al, 2012[107]	N=307 40% male Age at diagnosis: 0–3 years Age at evaluation: Mean 18.1 years	N=97 siblings	Cocaine/crack rates for current use were 0.6% in survivors vs 1.0% in siblings and 1.6% in survivors vs. 3.1% in siblings for past use	Poor mental health score
Diet	Zhang et al, 2016[108]	N=2570 51.6% male Age at diagnosis: Mean 8.3 years Age at evaluation: Mean 32.3 years	None	Low mean Healthy Eating Index 2010 score of 57.9 out of 100; 15%, 8%, 31% and 34% (respectively) met the recommended intake for fiber, potassium, magnesium and calcium	Sarcoma diagnosis; <5 years at diagnosis; cumulative glucocorticoid dose ≥9000 mg/m^2
	Smith et al, 2014[109]	N=1598 49.2% male Age at diagnosis: Median 7.9 years Age at evaluation: Median 32.7 years	None; compared to AICR guidelines	74% and 53% did not consume recommended fruit and vegetables, and complex carbohydrates; 90% and 70% consumed over red meat and sodium recommendation	Survivors with metabolic syndrome
	Belle et al, 2017[110]	N=1864 52% male Age at diagnosis: Mean 8.8 years Age at evaluation: Mean of 17.2 years since diagnosis	N=698 siblings N=8258 population controls in the Swiss Health Survey	93%, 57% and >80% CCS did not meet national dietary guidelines for fruit and vegetable consumption, meat, and dairy intake. Control adherence was equally poor	Female sex, higher education, higher parental education and sport participation were associated with improved adherence
Physical Activity	Wilson et al, 2014[99]	N=7287 49% male	N=2107 Siblings	47.5% of survivors vs 41.5% of siblings did not meet CDC physical activity guidelines; 19.0% of	Female sex; older age at survey; black race; lower educational attainment

Health Behavior	Source	Survivor Population	Comparison Group	Findings	Risk Factors Identified in Survivors*
		Age at diagnosis: <21 years Age at evaluation: Median 36.1 years		survivors reported decline in physical activity vs. 17.6% in siblings	
	Hocking et al, 2013[111]	N=117 36% male Age at diagnosis: <21 years Age at evaluation: Mean 21.6 years	N=148 Controls	CCS had lower exercise scores than comparison group members at baseline (43.57 vs. 51.68) and 2-month follow-up (42.73 vs. 60.16)	Survivor reported health problems; low-self efficacy
	Ness et al, 2009[98]	N=9301 50.7% male Age at diagnosis: <21 years Age at evaluation:	N=2886 siblings	52.1% survivors vs 47% of siblings did not meet CDC guidelines for physical activity; 22.7% survivors vs 14.0% siblings were inactive	Female sex; black race; older age; unable to work; underweight or obese; smoking
Sun Exposure	Levy-Shraga et al, 2015[112]	N=143 46.9% male Age at diagnosis: <21 years Age at evaluation: Mean 11.2 years	N=150 non-cancer patients of primary care pediatric clinics	CCS reported 94 minutes of sun exposure/day; controls reported 81 minutes/day; 39.4% CCS reported wearing sunscreen vs. 38% in controls	Ultra-orthodox religion; older age associated with less sunscreen use
	Krull et al, 2011[86]	N= 6440 49% male Age at diagnosis: <21 years Age at evaluation: Mean 32.0 years	None	44.4% CCS reported wearing sunscreen; 33.2% of those recommended to get skin exam, received an exam	Older survivors and diagnosis of brain tumor more likely to wear sunscreen; older survivors and income ≥20,000 more likely to get skin exam
Risky Sexual Behavior / HPV	Klosky et al, 2017[113]	N=982 54.6% male Age at diagnosis: Median 12.2 years Age at evaluation: Median 16.3 years	Compared to two population cohorts: NHIS and NIS-Teen	23.8% CCS vs. 40.5% in general population initiated HPV-vaccination; 13.5% CCS vs 20.8% general population completed vaccination	No provider recommendation; health insurance coverage knowledge; male sex; younger age; perceived barriers
	Klosky et al, 2014[114]	N=307 40% male Age at diagnosis: 0–3.76 years Age at evaluation: Mean 18.1 years	None	5% of survivors reported no protection against pregnancy at last intercourse; 10% reported no protection against STDs	Cancer type, time since diagnosis, alcohol use and peer influences

*Unless otherwise specified, listed risk factors all increased the likelihood of the discussed health behavior.

CCS=Childhood cancer survivor; CCSS=Childhood Cancer Survivor Study; NHIS=National Health Interview Survey; SJLIFE=St. Jude Lifetime Cohort Study; OR=odds ratio; 95% CI=95% Confidence interval; AICR=American Institute for Cancer Research; STDs=Sexually transmitted diseases; NIS-Teen=National Immunization Survey-Teen